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U1S S1317 S1318 S1321 S2413 S2415 S2416 S2418

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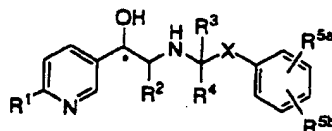
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(54) Selective β_3 agonists for the treatment of diabetes and obesity

(57) Compounds of formula



I

as defined in claim 1, and prodrugs thereof, are selective β_3 adrenergic receptor agonists with very little β_1 and β_2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents.

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TITLE OF THE INVENTION

SELECTIVE β_3 AGONISTS FOR THE TREATMENT OF DIABETES
AND OBESITY

5 BACKGROUND OF THE INVENTION

β -Adrenoceptors have been subclassified as β_1 and β_2 since 1967. Increased heart rate is the primary consequence of β_1 -receptor stimulation, while bronchodilation and smooth muscle relaxation typically result from β_2 stimulation. Adipocyte lipolysis was initially
10 thought to be solely a β_1 -mediated process. However, more recent results indicate that the receptor-mediating lipolysis is atypical in nature. These atypical receptors, later called β_3 -adrenoceptors, are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis (breakdown of fat) and energy expenditure.

15 Early developments in this area produced compounds with greater agonist activity for the stimulation of lipolysis (β_3 activity) than for stimulation of atrial rate (β_1) and tracheal relaxation (β_2). These early developments disclosed in Ainsworth *et al.*, U.S. Patents 4,478,849 and 4,396,627, were derivatives of phenylethanolamines.

20 Such selectivity for β_3 -adrenoceptors could make compounds of this type potentially useful as antiobesity agents. In addition, these compounds have been reported to show antihyperglycemic effects in animal models of non-insulin-dependent diabetes mellitus.

25 A major drawback in treatment of chronic diseases with β_3 agonists is the potential for stimulation of other β -receptors and subsequent side effects. The most likely of these include muscle tremor (β_2) and increased heart rate (β_1). Although these phenylethanolamine derivatives do possess some β_3 selectivity, side effects of this type have
30 been observed in human volunteers. It is reasonable to expect that these side effects resulted from partial β_1 and/or β_2 agonism.

More recent developments in this area are disclosed in Ainsworth *et al.*, U.S. Patent 5,153,210, Caulkett *et al.*, U.S. Patent

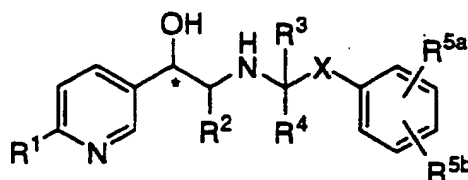
4,999,377, Alig *et al.*, U.S. Patent 5,017,619, Lecount *et al.*, European Patent 427480 and Bloom *et al.*, European Patent 455006.

Even though these more recent developments purport to describe compounds with greater β_3 selectivity over the β_1 and β_2 activities, this selectivity was determined using rodents, in particular, rats as the test animal. Because even the most highly selective compounds, as determined by these assays, still show signs of side effects due to residual β_1 and β_2 agonist activity when the compounds are tested in humans, it has become apparent that the rodent is not a good model for predicting human β_3 selectivity.

Recently, assays have been developed which more accurately predict the effects that can be expected in humans. These assays utilize cloned human β_3 receptors which have been expressed in Chinese hamster ovary cells. See J.G. Granneman *et al.*, *Mol. Pharmacol.*, 1992, 42:964-970; Emorine *et al.*, *Science*, 1989, 245:1118-1121; and Liggett, *Mol. Pharmacol.*, 1992, 42:634-637. The agonist and antagonist effects of the various compounds on the cultivated cells provide an indication of the antiobesity and antidiabetic effects of the compounds in humans.

SUMMARY OF THE INVENTION

The instant invention is concerned with compounds of Formula I



I

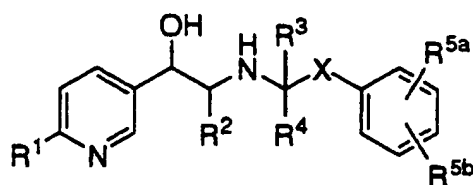
which are useful as antiobesity and antidiabetic compounds. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the compounds of Formula I. A still further object is to describe processes for the

preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

5

DESCRIPTION OF THE INVENTION

The present invention provides compounds having the Formula I:

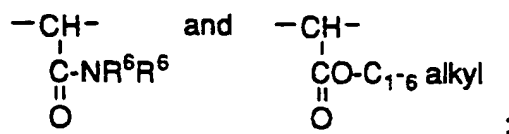


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I

and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

15 X is a bond or is selected from (CH₂)_n-, -CH(CN)-,



n is selected from 1, 2 and 3;

m is selected from zero, 1, 2 and 3;

20 p is selected from zero, 1 and 2;

R¹ is selected from

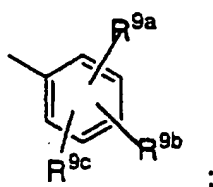
- (1) -H,
- (2) -OH,
- (3) halogen,
- (4) -NR⁸R⁸,
- (5) -NR⁸COR⁹,
- (6) -NR⁸COH,

25

- (7) $-\text{NR}^8\text{SO}_2\text{R}^9$, and
 (8) $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{C}_{1-10}\text{ alkyl}$;

R^2 is independently selected at each occurrence from -H and -C₁₋₆ alkyl;

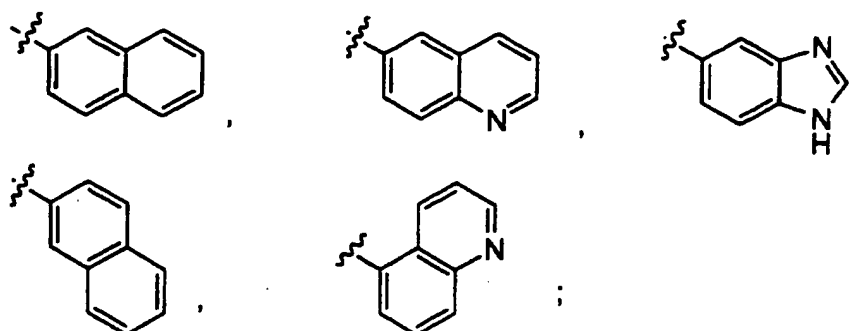
R^3 is selected from -H, -C₁₋₁₂ alkyl, heterocycle and



R^4 is selected from -H, -C₁₋₁₂ alkyl, -CN, -CONR⁶R⁶ and -COOC₁₋₆ alkyl;

R^{5a} , R^{5b} , R^{9a} , R^{9b} , and R^{9c} are each independently selected from:

- (1) -H, -C₁₋₁₂ alkoxy, -C₁₋₆ alkyl, halogen, -OH, -CN, $-(\text{CH}_2)_m\text{N}(\text{R}^2)\text{COC}_{1-6}\text{ alkyl}$, $-\text{CON}(\text{R}^2)\text{R}^2$, $-\text{CON}(\text{R}^2)\text{OR}^2$, $-\text{CO}_2\text{R}^2$, $-\text{S}(\text{O})_p\text{-C}_{1-6}\text{ alkyl}$, $-\text{N}(\text{R}^2)\text{SO}_2\text{R}^7$, $-\text{N}(\text{R}^2)\text{R}^2$, $-\text{OCH}_2\text{CON}(\text{R}^2)\text{R}^2$, $-\text{OCH}_2\text{CO}_2\text{-C}_{1-6}\text{ alkyl}$, aryl, $-\text{CF}_3$ and $-\text{CH}_2\text{Y}$ wherein Y is selected from -CN, -C₁₋₁₂ alkoxy, $-\text{CON}(\text{R}^2)\text{R}^2$, $-\text{CO}_2\text{R}^2$ and $-\text{N}(\text{R}^2)\text{SO}_2\text{R}^7$; or
- (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring, such as for example



or

- (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring;

R⁶ is independently selected at each occurrence from:

-H, -C₁₋₁₂ alkyl, -C₃₋₆ cycloalkyl, aralkyl, aryl and heterocycle, or both R⁶ groups together with the nitrogen to which they are attached may form a 5-10 membered heterocycle;

R⁷ is selected from C₁₋₆ alkyl, aryl and aralkyl;

R⁸ is independently selected at each occurrence from -H and C₁₋₁₀ alkyl;

R⁹ is selected from C₁₋₁₀ alkyl and -NR⁸R⁸;

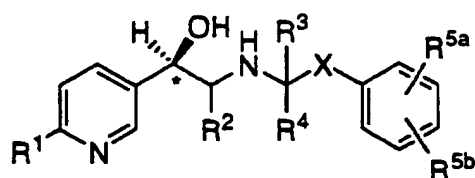
aryl is selected from phenyl, 1-naphthyl and 2-naphthyl and is unsubstituted or mono- or di-substituted, wherein the substituents are independently selected at each occurrence from R^{5a}; and

heterocycle is an unsubstituted or mono- or di-substituted group selected from:

- (1) a 5 or 6-membered saturated or unsaturated heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and
- (2) a benzene ring fused to a saturated or unsaturated 5 or 6-membered heterocyclic ring comprised of

5 carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and wherein substituents on the heterocycle are independently selected at each occurrence from nitro, keto, azo, thiazo, and R^{5a}.

In one embodiment of the present invention are compounds of Formula I which have the Formula Ia:

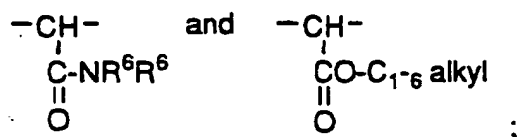


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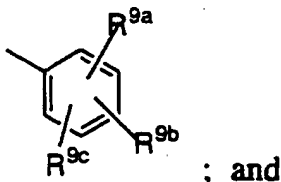
and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is a bond or is selected from -(CH₂)-, -CH(CN)-,



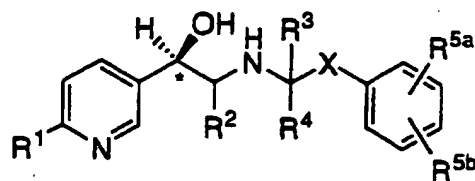
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R³ is selected from -H, -C₁₋₁₂ alkyl and



20 R^{5a} and R^{5b} are each independently selected from: -H, halogen, -C₁₋₁₂ alkoxy, -C₁₋₆ alkyl, -CON(R²)R² and -CON(R²)OR².

In a second embodiment of the instant invention are compounds of Formula I which have the Formula Ia:



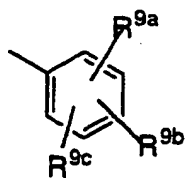
Ia

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and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is a bond;

R³ is



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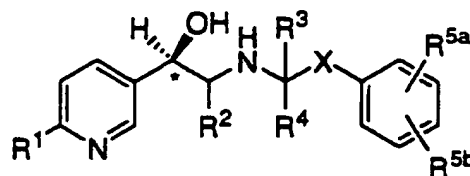
R⁴ is selected from -H, and -C₁₋₁₂ alkyl; and

R^{5a} and R^{9a} are each independently selected from:

- (1) -C₁₋₁₂ alkoxy, -OH, -CN, -CON(R²)R², -CON(R²)OR², and -CH₂Y wherein Y is selected from -CN, -C₁₋₁₂ alkoxy, -CON(R²)R², -CO₂R² and -N(R²)SO₂R⁷; or
- (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring, or
- (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring.

25

In a third embodiment of the instant invention are compounds of Formula I which have the Formula Ia:



Ia

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and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

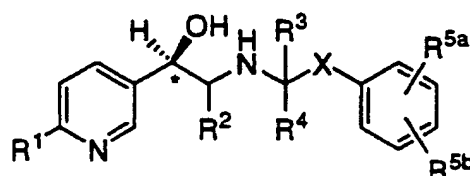
X is a bond;

R³ is selected from -H and -C₁-12 alkyl;

10 R⁴ is -CON(R⁶)R⁶; and

R^{5a} is selected from: -C₁-12 alkoxy, -OH, -CN, -CON(R²)R², and -CON(R²)OR².

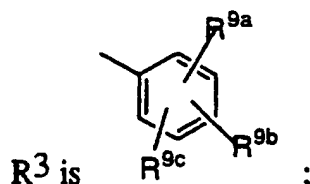
15 In a fourth embodiment of the instant invention are compounds of Formula I which have the Formula Ia:



Ia

20 and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is -(CH₂)-;



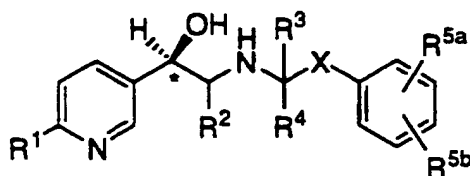
R⁴ is selected from -H, -C₁-12 alkyl, -CN and -CON(R⁶)R⁶; and

R^{5a} is selected from -H, halogen and -CF₃; and

R^{9a} is selected from

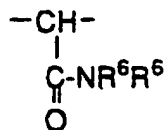
- 5 (1) -CN, -CON(R²)R², -CON(R²)OR², -OH, -C₁-6 alkyl and -C₁-12 alkoxy; or
- (2) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle
- 10 ring.

In a fifth embodiment of the instant invention are compounds of Formula I which have the Formula Ia:



Ia

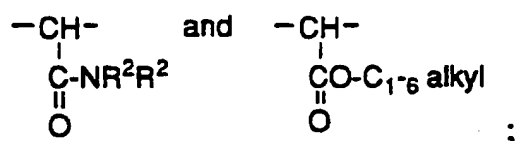
and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:



- X is selected from -CH(CN)- and ;
- 20 R³ and R⁴ are independently selected from -H and -C₁-12 alkyl; and
 - R^{5a} is selected from: -C₁-12 alkoxy, -OH, -CN, -CON(R²)R² and -CON(R²)OR².

In a sixth embodiment of the instant invention are compounds of Formula I wherein:

X is a bond or is selected from $-(CH_2)_n-$, $-CH(CN)-$,



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n is selected from 1, 2 and 3;

m is selected from zero, 1, 2 and 3;

p is selected from zero, 1 and 2;

R¹ is selected from

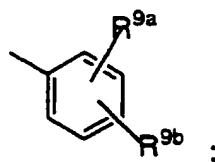
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- (1) -H,
- (2) -OH,
- (3) halogen,
- (4) $-NR^8R^8$,
- (5) $-NR^8COR^9$,
- 15 (6) $-NR^8COH$,
- (7) $-NR^8SO_2R^9$, and
- (8) $-N(R^8) \underset{\text{O}}{\underset{||}{CO}} - C_{1-10} \text{ alkyl};$

15

R² is independently selected at each occurrence from -H and $-C_{1-6} \text{ alkyl};$

20 R³ is selected from -H, substituted $-C_{1-12} \text{ alkyl}$, heterocycle and



R⁴ is selected from -H, $-C_{1-12} \text{ alkyl}$, -CN, $-CON(R^2)R^2$ and $-COOC_{1-6} \text{ alkyl};$

25 R^{5a}, R^{5b}, R^{9a} and R^{9b} are each independently selected from:

- (1) -H, -C₁₋₁₂ alkoxy, -C₁₋₆ alkyl, halogen, -OH, -CN, -(CH₂)_mN(R²)COC₁₋₆ alkyl, -CON(R²)R², -CO₂C₁₋₆ alkyl, -S(O)_p-C₁₋₆ alkyl, -N(R²)SO₂R⁷, -N(R²)R², -OCH₂CON(R²)R², and -OCH₂CO₂-C₁₋₆ alkyl; or
- 5 (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a heterocycle ring, or
- (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a heterocycle ring;
- 10

R⁶ is independently selected at each occurrence from:

- H, -C₁₋₁₂ alkyl, -C₃₋₆ cycloalkyl, aralkyl, aryl and heterocycle, or both R⁶ groups together with the nitrogen to which they are attached may form a 5-10 membered heterocycle;
- 15

R⁷ is selected from C₁₋₆ alkyl, aryl and aralkyl;

R⁸ is independently selected at each occurrence from -H and C₁₋₁₀ alkyl;

20 R⁹ is selected from C₁₋₁₀ alkyl and -NR⁸R⁸;

aryl is selected from phenyl, 1-naphthyl and 2-naphthyl and is unsubstituted or mono- or di-substituted, wherein the substituents are independently selected at each occurrence from R^{5a}; and

25 heterocycle is an unsubstituted or mono- or di-substituted group selected from:

- (1) a 5 or 6-membered saturated or unsaturated heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and
- 30 (2) a benzene ring fused to a saturated or unsaturated 5 or 6-membered heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-,

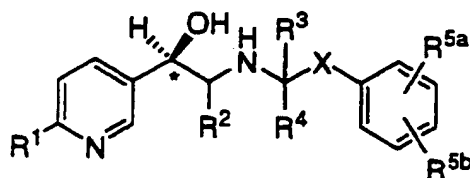
and wherein substituents on the heterocycle are independently selected at each occurrence from nitro, keto, azo, thiazo, and R^{5a}.

- 5 Representative compounds of the present invention include but are not limited to the following:
- N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- 10 N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- α -[[[(R)-2-hydroxy-2-(pyridin-3-yl)ethyl]amino]methyl]-N,N-dimethylbenzeneacetamide;
- α -[[[(R)-2-hydroxy-2-(2-chloropyrid-5-yl)ethyl]amino]methyl]-N,N-dimethylbenzeneacetamide;
- 15 (R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- (R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- (R),(R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- 20 (R),(R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- (R),(S)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- 25 (R),(S)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(6-aminopyridin-3-yl)-ethylamine; and
- (R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(6-aminopyridin-3-yl)-ethylamine.
- 30

Combinations of substituents and/or variables within Formula I are permissible only if such combinations result in stable compounds.

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural Formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule, in particular, R³ and R⁴. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the hydroxy substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the hydroxy substituent is below the plane of the structure.

The following stereospecific Structure Ia, wherein R¹, R², R³, R⁴, R^{5a}, R^{5b}, and X are as defined in Formula I, represents the preferred stereoisomers of the instant invention:



Ia

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Throughout the instant application, the following terms have the indicated meanings either individually (e.g. alkyl) or as part of a larger group (e.g., as in aralkyl or -OCH₂CO₂-C₁₋₆ alkyl).

As used herein the terms "alk" and "alkyl" have the same meaning and are intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, e.g., methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl (Pn), hexyl (hex), heptyl, octyl, nonanyl, decyl, undecyl and dodecyl, and the isomers thereof such as isopropyl (i-Pr), isobutyl (i-Bu), secbutyl (s-Bu), tertbutyl (t-Bu), isopentyl,

30

isohexyl and the like. The terms "alk" and "alkyl" further include both unsubstituted and mono-, di- and tri-substituted hydrocarbon groups as defined above wherein the substituents are independently selected from the group consisting of: halogen (especially to form trihaloalkyl, particularly trichloromethyl or trifluoromethyl), aryl, C₃-6cycloalkyl, hydroxy, amino, thiol, -CN, C₁-12 alkoxy, -CON(R²)R², -CO₂R², and -N(R²)SO₂R⁷. Alkyl groups of Formula I which are defined as having from 1 to 12 carbon atoms preferably contain from 1 to 8 carbon atoms.

The term "cycloalkyl" is intended to include cyclized alkyl chains having the specified number of carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

"Alkoxy" represents an alkyl group having the indicated number of carbon atoms attached through an oxygen bridge, e.g., methoxy, ethoxy, propyloxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and the like.

The terms "halogen" and "halo" have the same meaning and are intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

Aryl is defined above in Formula I. Phenyl and mono- or disubstituted phenyl are preferred.

The term "aralkyl" is intended to mean -C₁-12 alkyl-aryl, wherein the terms alkyl and aryl are as defined above. In particular, aralkyl includes benzyl (Bz).

Heterocycle is defined above in Formula I. The monocyclic and bicyclic heterocycles described above are unsubstituted, or mono- or di-substituted on any available carbon atoms. The heterocyclic ring may be attached within structural Formula I by any carbon atom or heteroatom, e.g., N, in the ring which results in the creation of a stable structure.

Examples of 5 and 6-membered heterocycles and fused heterocycles include pyridyl, quinolinyl, pyrimidinyl, pyrrolyl, thienyl, imidazolyl, thiazolyl, benzimidazolyl, thiadiazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl,

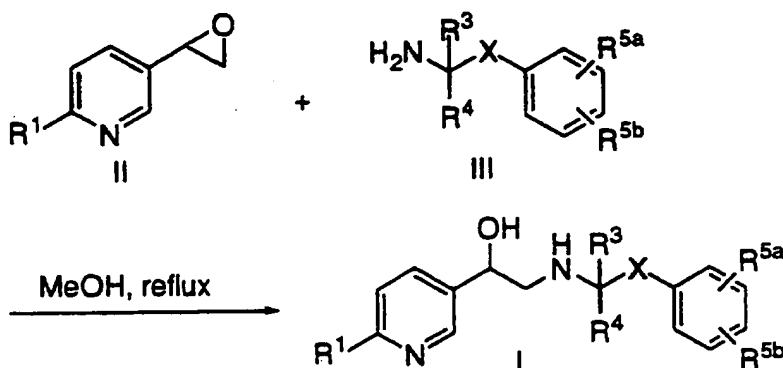
benzofuranyl, benzoxazinyl, benzisoxazolyl, benzothiazolyl, tetrahydronaphthyl, dihydrobenzofuranyl, tetrahydroquinolyl, furopyridine and thienopyridine. Preferred monocyclic heterocycles include 2- and 3-thienyl, 2- and 3-furyl, 2-, 3- and 4-pyridyl, and
 5 imidazolyl. Preferred bicyclic heterocycles include 4-, 5-, 6- or 7-indolyl, 4-, 5-, 6- or 7-isindolyl, 5-, 6-, 7- or 8-quinolyl, 5-, 6-, 7- or 8-isoquinolyl, 4-, 5-, 6- or 7-benzothiazolyl, 4-, 5-, 6- or 7-benzoxazolyl, 4-, 5-, 6- or 7-benzimidazolyl, 4-, 5-, 6- or 7-benzoxadiazolyl, 4-, 5-, 6- or 7-benzofuranzanyl, 4-, 5-, 6- or 7-
 10 benzodioxolyl, and 4-, 5-, 6- or 7-benzofuran.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, $N(R^6)R^6$ may represent NH_2 , $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

15 The compounds of Formula I of the present invention can be prepared from the epoxide intermediates such as those of Formula II and the amine intermediates such as those of Formula III. Preparation of these intermediates is described in the following schemes. The variables used in the schemes (e.g., R^1 , R^2 , R^3 , etc.) are as defined in
 20 Formula I unless otherwise noted.

Intermediates II and III are coupled by heating them neat or as a solution in a polar solvent such as methanol, acetonitrile, tetrahydrofuran, dimethylsulfoxide or N-methyl pyrrolidine for 1 to 24 hours at the temperature of 30 to 150°C to provide compounds I as
 25 shown in Scheme 1. The reaction is conveniently conducted in refluxing methanol. Alternately, a salt of amine III, such as the trifluoroacetate or hydrochloride salt, may be used. In these cases, a base such as sodium bicarbonate or diisopropylethylamine is added to the reaction mixture. The product is isolated by recrystallization, trituration,
 30 preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still, *et al.*, *J. Org. Chem.* 43, 2923 (1978), medium pressure liquid chromatography, or HPLC. Compounds which are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

SCHEME 1



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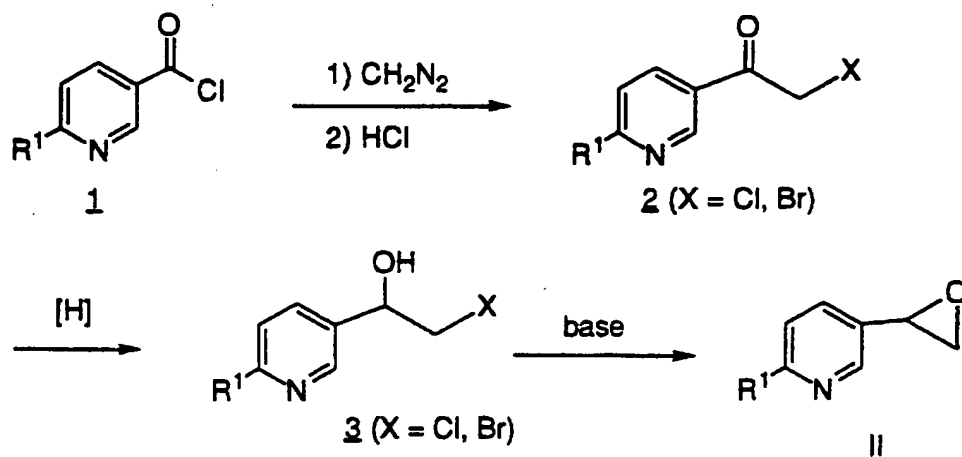
Epoxides of Formula II are known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 2. Acid chloride 1, which may be commercially available or readily prepared from the corresponding acid by treatment with, for example, thionyl chloride or oxalyl chloride, is treated with diazomethane in a solvent such as diethyl ether. The resultant diazoketone is then treated with hydrogen chloride for example to give chloroketone 2 (X = Cl). The haloketone 2 is then reduced with a reducing agent such as sodium borohydride. The resultant alcohol 3 is treated with base such as potassium carbonate in refluxing acetone to provide the desired epoxide II. The enantiomerically enriched (*R*) and (*S*) epoxides II are readily available by asymmetric reduction of haloketones 2 using chiral reducing agents such as (-) or (+)-DIP-Cl, (*R*) or (*S*)-Alpine borane or (*R*) or (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole-borane ((*R*) or (*S*)-OAB•BH₃).

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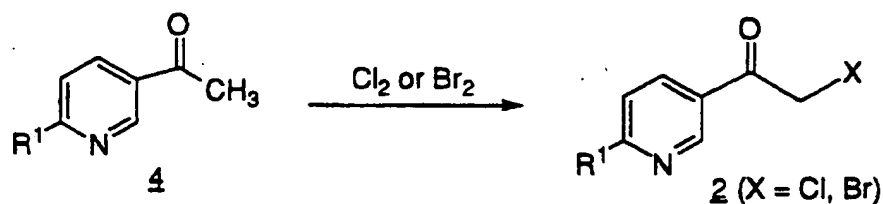
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SCHEME 2



- 5 An alternate route to the desired haloketones 2 is illustrated in Scheme 3. Methylketone 4 may be converted to the corresponding haloketone using a variety of reagents known to those in the art and summarized in Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, 369-372. Conveniently, methylketone 4 is treated
- 10 with chlorine or *N*-chlorosuccinimide in acetic acid with an additional acid source such as hydrogen chloride or aluminum chloride. For the synthesis of 2 wherein $\text{X} = \text{Br}$, bromine, dibromobarbituric acid or NBS with hydrogen bromide or aluminum bromide may be used. In some cases, the chloro or bromoketones 2 may be commercially
- 15 available.

SCHEME 3

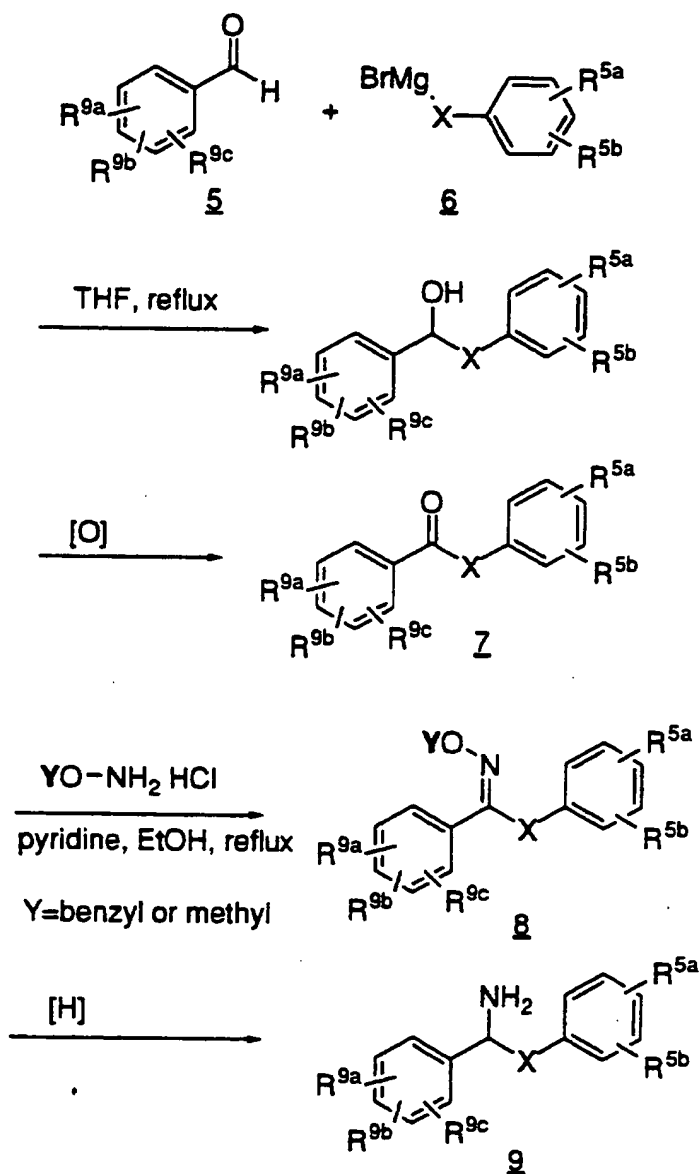


Many of the methylketones 4 are commercially available or readily prepared by methods described in the literature and known to those skilled in the art. When R¹ is -NH₂ on the acid chloride 1 or methylketone 4 it may need to be protected during the subsequent
5 procedures. A description of such protecting groups may be found in: *Protective Groups in Organic Synthesis*, 2nd Ed., T. W. Greene and P. G. M. Wuts, John Wiley and Sons, New York, 1991.

Preparation of compounds of Formula III is described by Washburn, *et al* in European Patent application 0 659 737 A2 (published
10 June 28, 1995) and references cited therein. An example is illustrated in Scheme 4 for the preparation of intermediate amine 2 (compound III wherein R³= phenyl and R⁴=H). The appropriate aldehyde 5 in a solvent such as tetrahydrofuran or diethyl ether is reacted with an organometallic reagent 6 to generate the corresponding alcohol which
15 upon treatment with an oxidant such as chromic acid in solvent such as aqueous acetone gives compound 7. The ketone group is converted to an O-alkyl or O-benzyl oxime, conveniently by treatment with O-alkyl or O-benzyl hydroxyamine hydrochloride in ethanol at reflux in the presence of a base such as pyridine or triethylamine. Reduction of
20 oxime ethers 8 with a reducing agent such as diborane gives the amine 2. Optically active compounds of Formula III can be obtained by reduction of oxime ethers 8 with a preequilibrated complex of the borane and enantiomerically pure norephedrine following the method of Y. Sakito *et al.*, *Tet Lett.*, 29, 223 (1988).

25

SCHEME 4

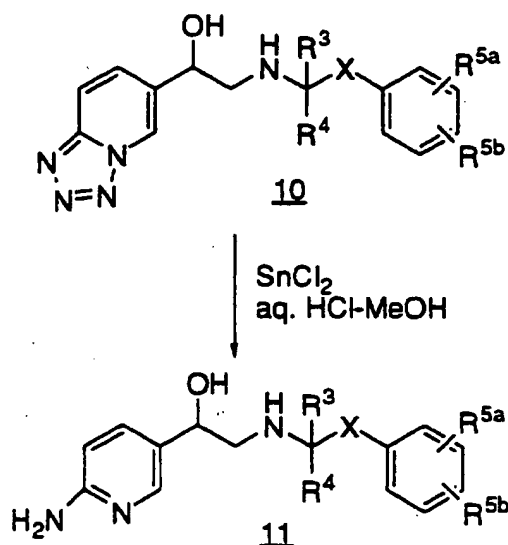


5 In some cases, the compound produced from the reaction of the intermediate epoxide and the intermediate amine may be further modified to form compounds within Formula I, for example, by the

removal of protecting groups or the manipulation of substituents, in particular, the R^1 substituent. In addition, manipulation of substituents on any of the intermediates in the reaction sequence illustrated in Scheme 1 may occur. One such example is illustrated in Scheme 5.

- 5 Compound 10 which is prepared as outlined in Scheme 1 from the corresponding epoxide, is subjected to reduction using tin(II) chloride to provide compound 11. Other examples of the substituents on Compound I which may be reduced to the corresponding amine by methods commonly known to those skilled in the art include nitro
- 10 groups, nitriles, and azides.

SCHEME 5



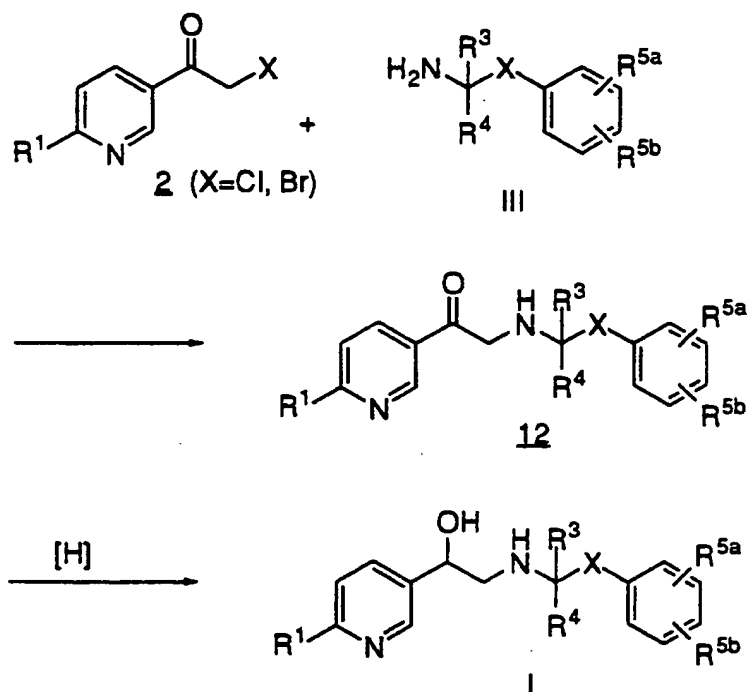
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- The Compounds I of the present invention can also be prepared from amine intermediates such as those of Formula III and haloketone intermediates such as those of Formula 2 as shown in Scheme 6. Amine III is alkylated with haloketone derivative 2, conveniently by treatment of a mixture of III and 2 in the presence of base such as potassium carbonate or triethylamine in a polar solvent such as acetonitrile, acetone or dimethylformamide. The resulting aminoketone
- 20

12 is reduced with a hydrogen source such as sodium borohydride in ethanol to give the desired aminoalcohol I.

SCHEME 6

5



In some cases, the product I from the reaction described in Scheme 6 may be further modified, for example, by removal of protecting groups or the manipulation of substituents, in particular the R¹ substituent. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skills in art.

An alternate synthesis of compounds of Formula I is illustrated in Scheme 7. The alcohol intermediate 3 is protected, for example, as its t-butyldimethylsilyl ether to give TBS derivative 13. This compound is then treated with amine III and a base such as diisopropylethylamine in a solvent, typically polar aprotic such as

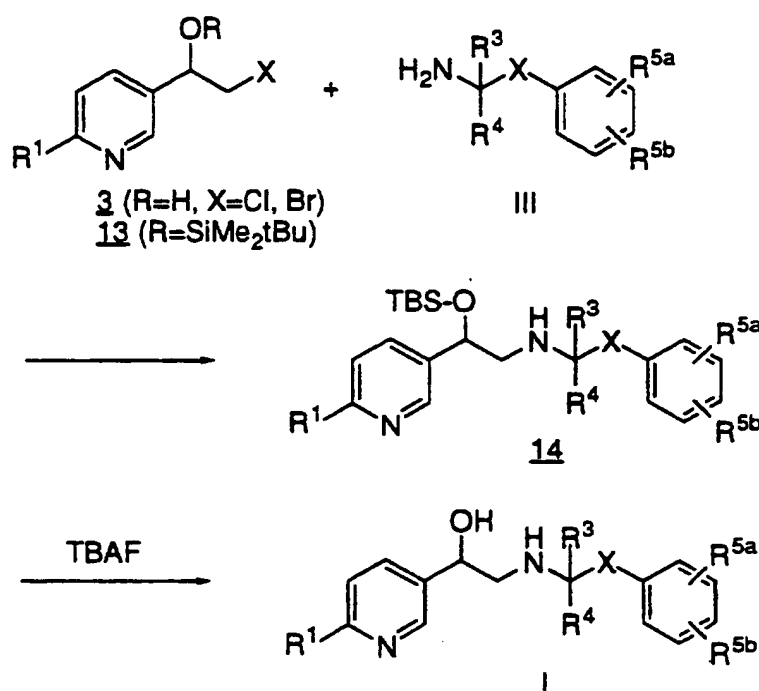
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acetonitrile, at temperatures of 25 to 150°C for 1 to 72 hours.

Typically, an iodide source such as sodium iodide is added to facilitate the reaction. The protecting group is then removed, in the cases of silyl ether, by treatment of the resulting amine 14 with a fluoride source such as tetrabutylammonium fluoride.

SCHEME 7



10

Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

15

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

5 The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a
10 carboxy, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases. In addition, the instant invention also encompasses prodrug forms of the compounds of Formula I where such forms can be made. For example, prodrug forms
15 may include pharmaceutically acceptable esters of Formula I compounds which contain an available hydroxy or carboxy group.

The present invention provides a compound of Formula I for use as an active therapeutic substance. In one aspect, the present invention provides a compound of Formula I for use in the treatment of
20 obesity in human or non-human animals. The present invention further provides a compound of Formula I for use in the treatment of hyperglycemia (diabetes) in human or non-human animals.

The disease diabetes mellitus is characterized by metabolic defects in production and utilization of glucose which result in the
25 failure to maintain appropriate blood sugar levels. The result of these defects is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and
30 dietary therapies.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes, often

occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese.

In addition the compounds of the present invention lower
5 triglyceride levels and cholesterol levels and raise high density lipoprotein levels and are therefore of use in combatting medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hyper-
triglyceridaemia, hypercholesterolaemia and conditions of low HDL
10 (high density lipoprotein) levels in addition to the treatment of atherosclerotic disease such as of coronary, cerebrovascular and peripheral arteries, cardiovascular disease and related conditions.

Accordingly, in another aspect the present invention provides a method of lowering triglyceride and/or cholesterol levels
15 and/or increasing high density lipoprotein levels which comprises administering, to a human or a non-human animal in need thereof, a therapeutically effective amount of a compound of the Formula (I) or pharmaceutically acceptable salt thereof. In a further aspect the present invention provides a method of treating atherosclerosis which comprises
20 administering, to an animal in need thereof; a therapeutically effective amount of a compound of the Formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed below for treating diabetes and obesity and they may also contain other active agents
25 known for use in the treatment of atherosclerosis and related conditions.

The compounds of Formula I may be administered in combination with other therapeutically active agents known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of
30 cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin, pravastatin and fluvastatin; HMG-CoA-synthase inhibitors, squalene epoxidase inhibitors and squalene synthase inhibitors; inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for

example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linked dextran; nicotiny alcohol, nicotinic acid or a salt thereof; vitamin E; thyromimetics; and niacin; and probucol .

5 For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

10 The compounds of the instant invention also have the effect of reducing intestinal motility and thus find utility as aiding in the treatment of various gastrointestinal disorders such as irritable bowel syndrome. It has been proposed that the motility of non-sphincteric smooth muscle contraction is mediated by activity at β_3 adrenoreceptors. The availability of a β_3 specific agonist, with little
15 activity at β_1 and β_2 receptors will assist in the pharmacologic control of intestinal motility without concurrent cardiovascular effects. The instant compounds are administered generally as described below with dosages similar to those used for the treatment of diabetes and obesity.

20 It has also been found unexpectedly that the compounds which act as agonists at β_3 adrenoreceptors may be useful in the treatment of gastrointestinal disorders, especially peptic ulcerations, esophagitis, gastritis and duodenitis, (including that induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal
25 ulcerations.

 In addition, β_3 receptors have been indicated to have an effect on the inhibition of the release of neuropeptides in certain sensory fibers in the lung. As sensory nerves may play an important role in the neurogenic inflammation of airways, including cough, the instant
30 specific β_3 agonists may be useful in the treatment of neurogenetic inflammation , such as asthma, with minimal effects on the cardio-pulmonary system.

β_3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β_3 receptors in the brain and

thus an additional contemplated utility of the compounds of this invention are as antidepressant agents.

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with
5 an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual
10 administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to
15 about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may
20 vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating diabetes mellitus and/or hyperglycemia generally satisfactory results are obtained when the compounds of the
25 present invention are administered at a daily dosage of from about 0.001 milligram to about 10 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to
30 about 700 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily

dosage of from 0.01 milligram to about 100 milligrams per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about
5 0.7 milligrams to about 7000 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch,
10 potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to
15 modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

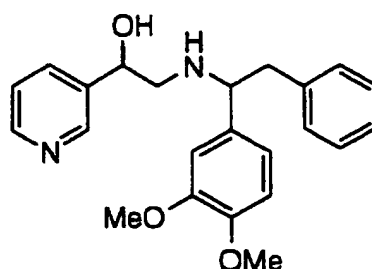
20 These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary
25 conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or
30 dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example,

water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The following examples are provided so that the invention might be more fully understood. They should not be construed as
5 limiting the invention in any way.

EXAMPLE 1



10

Preparation of N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethanamine

Step A: N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethanamine
15

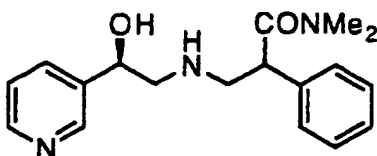
To a solution of α -(3,4-dimethoxyphenyl)-benzenethanamine (see Washburn *et al.*, EP 0 659 737 A2 for the preparation of this compound) (257 mg, 1 mmol, 2 eq) in anhydrous acetonitrile (10 mL) is added a solution of 2-chloro-5-(2-bromoacetyl)pyridine (prepared as described in Example 3) (111 mg, .5 mmol) at 0°C under a
20 nitrogen atmosphere. The mixture is allowed to warm to room temperature and stirred for 1 h. To this mixture is added a solution of sodium borohydride (110 mg, 2.9 mmol, 5.8 eq) in abs. ethanol at room temperature. After one hour, the excess sodium borohydride is
25 quenched with 1N HCl to pH 4.0 and then ethanol amine (0.28 mL, 4.5 mmol, 8 eq) is added. After stirring for 10 minutes, the mixture is diluted with ethyl acetate (30 mL). The organic layer is washed with

brine, dried over anhydrous sodium sulfate and then concentrated.
Purification by silica column gives the desired compound.

5 Step B: N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(pyridin-3-yl)-ethylamine

A solution of N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethylamine (100 mg, .26 mmol) in ethanol (7 mL) with 5 N sodium hydroxide (0.1 mL, .5 mmol) is degassed with argon prior to addition of Ni(R) (100 mg). The mixture is hydrogenated at 40 Psi for overnight and then the catalyst is filtered through Celite and washed with a small amount of ethanol. Evaporation of the filtrate gives the title compound.

15 EXAMPLE 2



Preparation of α -[[[(R)-2-hydroxy-2-(pyridin-3-yl)ethyl]amino]-methyl]-N,N-dimethylbenzeneacetamide

20 Step A: α -[[[(R)-2-hydroxy-2-(2-chloropyrid-5-yl)ethyl]amino]-methyl]-N,N-dimethylbenzeneacetamide

A solution of α -(aminomethyl)-N,N-dimethylbenz-
acetamide (see Washburn *et al.*, EP 0 659 737 A2 for the synthesis of
25 this starting material) (384 mg, 2 mmol, 2 eq) and (R)-(2-chloropyrid-5-yl)oxirane (prepared as described in Example 3) (143 mg, 1 mmol) in dry methanol in a gas tight vessel is heated in an oil bath at 90°C overnight. The solvent is stripped and the product is isolated by silica column.

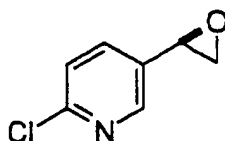
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Step B: α -[[*(R)*-2-hydroxy-2-(pyridin-5-yl)ethyl]amino]methyl]-
N,N-dimethylbenzeneacetamide

The title compound is prepared by utilizing the procedure described in Step B of Example 1.

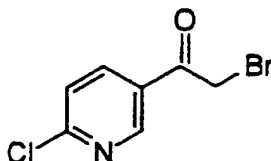
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EXAMPLE 3



10 Preparation of (*R*)-(2-chloropyrid-5-yl)oxirane

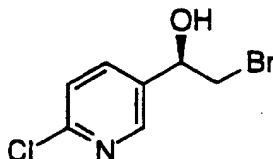
Step A: 2-Chloro-5-(2-bromoacetyl)pyridine



15 A solution of 784 mg of 2-chloro-5-acetylpyridine in 10 mL of tetrahydrofuran (THF) was added via canula to a solution of 1.44 g of dibromobarbituric acid (DBBA) in 10 mL of THF. The resultant solution was heated at 50-55°C for 12 h, and then an additional 0.72 g DBBA was added. After stirring at 50-55°C for 2.5 more hours, 0.36 g
20 DBBA was added. The mixture was allowed to stir for 2 h at which point NMR analysis of an aliquot indicated 87% conversion. The reaction mixture was cooled, diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash
25 chromatography (silica gel, 15% ethyl acetate/hexane) provided the desired compound as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.96

(d, 1H, J = 2.6 Hz), 8.21 (dd, 1H, J = 2.5, 8.3 Hz), 7.46 (d, 1H, J = 8.4 Hz), 4.37 (s, 2H).

Step B: (R)- α -Bromomethyl-3-(6-chloropyridine)methanol

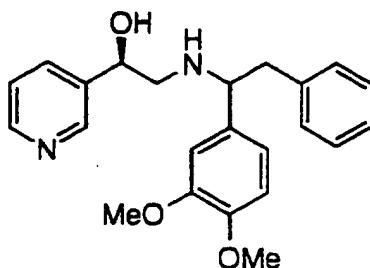


- 5
- To a solution of 602 mg (1.88 mmol) of (-)-DIP-Cl (diisopinocampheylchloroborane) in 0.5 mL of THF at -25°C was added via canula 200 mg of ketone from Step A in 1.5 mL of THF at -25°C.
- 10 The reaction mixture was allowed to stir at -25°C for 17 h. It was then quenched by the addition of water and extracted with ether. The ether phase was diluted with ethyl acetate, washed with two portions of saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulfate and concentrated. Purification by flash
- 15 chromatography (silica gel, 15 and 25% ethyl acetate/hexane) gave the desired compound: ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, 1H), 7.70 (dd, 1H), 7.32 (d, 1H), 4.97 (m, 1H), 3.61 (dd, 1H), 3.50 (dd, 1H), 2.85 (d, 1H).

20 **Step C:** (R)-(2-chloropyrid-5-yl)oxirane

- To a solution of 100 mg of bromoalcohol from Step B in 2 mL of 1:1 THF:water was added 1 mL of 5 N aqueous sodium hydroxide solution. The mixture was allowed to stir for 10 min. It was then extracted with three portions of dichloromethane. The combined
- 25 organic phases were washed with two portions of water and brine, dried over magnesium sulfate, and concentrated to give the title compound: ¹H NMR (400 MHz, CDCl₃) δ 8.34 (d, 1H), 7.48 (dd, 1H), 7.29 (d, 1H), 3.86 (dd, 1H), 3.18 (dd, 1H), 2.78 (dd, 1H).

EXAMPLE 4



5 Preparation of (R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethylamine

Step A: (R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethylamine

10 A solution of α -(3,4-dimethoxyphenyl)benzeneethanamine (257 mg, 1 mmol, 2 eq) and (R)-(2-chloropyrid-5-yl)oxirane (Example 3, 77 mg, 0.5 mmol) in dry methanol in a gas tight vessel was heated at reflux in an oil bath overnight. The reaction was cooled to room temperature and then the solvent was stripped under vacuum. The

15 yellow residue was purified by flash chromatography on silica gel (eluent: ethylacetate: hexanes:9:1) to give the adduct as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (m, 1H), 7.53 (m, 1H), 7.07-7.30 (m, 6H), 6.71-6.8 (m, 3H), 4.38-4.58 (m, 1H), 3.87 and 3.86 (s, 3H. OCH₃), 3.82 (s, 3H, OCH₃), 3.70-3.85 (m, 1H), 2.80-3.0 (m, 2H), 2.64-

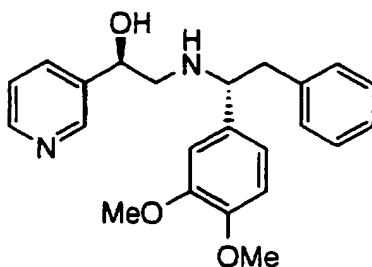
20 2.73 (m, 1H), 2.35-2.51 (m, 1H).

Step B: (R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(pyridin-3-yl)-ethylamine

A solution of (R)-N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(2-chloropyrid-5-yl)-ethylamine (100 mg, .26 mmol) in ethanol (7 mL) with 5 N sodium hydroxide (0.1 mL, .5 mmol) was degassed with argon prior to the addition of Ni(R) (100 mg). The mixture was hydrogenated at 40 Psi overnight and then the catalyst was filtered through Celite and washed with a small amount of ethanol. The filtrate was stripped and the product was purified by prep
 10 TLC on silica gel (eluent: 5% methanol in methylene chloride) to give the titled compound. ¹H NMR (500 MHz, CDCl₃) δ 8.47 (m, 2H), 7.58 (m, 1H), 7.01-7.32 (m, 6H), 6.79-6.84 (m, 3H), 4.53-4.67 (m, 1H), 3.89 and 3.88(s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.79-3.85 (m, 1H), 2.90-3.03 (m, 2H), 2.78 (m, 1H), 2.49-2.50 (m, 1H).

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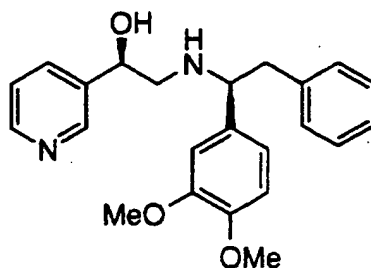
EXAMPLE 5



20 **Preparation of (R),(R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(pyridin-3-yl)-ethylamine**

Following the procedure outlined in Example 4, the title compound was prepared from the epoxide from Example 3 and (R)-α-(3,4-dimethoxyphenyl)benzeneethanamine: ¹H NMR (500 MHz, CDCl₃) δ 8.48 (d, 1H, J=4.8 Hz), 8.46 (s, 1H), 7.57 (dd, 1H, J=4.8, 1.4Hz), 7.09-7.31 (m, 6H), 6.77-6.83 (m, 3H), 4.49(t, 1H, J=7.2Hz),
 25 3.88(s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.78 (m, 1H), 2.88-3.0 (m, 2H), 2.78 (dd, 1H, J=4.8, 3.5 Hz), 2.57 (dd, 1H, J=13, 8Hz).

EXAMPLE 6

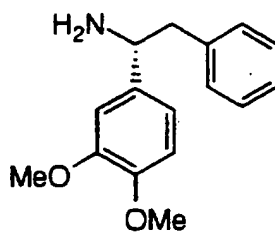


5 Preparation of (R),(S)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(pyridin-3-yl)ethanamine

Following the procedure outlined in Example 4, the title compound was prepared from the epoxide from Example 3 and (S)- α -(3,4-dimethoxyphenyl)benzeneethanamine (prepared as described in
 10 Example 7): ^1H NMR (500 MHz, CDCl_3) δ 8.48 (m, 2H) 7.57 (d, 1H $J=8$ Hz), 7.15-7.32 (m, 6H), 6.77-6.84 (m, 3H), 4.62 (dd, 1H, $J=9.2$, 3.3 Hz), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (m, 1H), 2.99 (dd, 1H, $J=13.5$, 5.5 Hz), 2.89 (dd, 1H, $J=13.5$, 8.5 Hz), 2.73 (dd, 1H, $J=11.5$, 3.3 Hz), 2.49 (dd, 1H, $J=11.5$, 9.2 Hz).

15

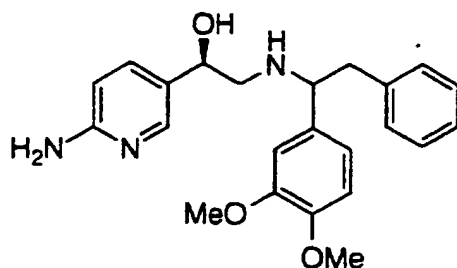
EXAMPLE 7



Preparation of (S)- α -(3,4-dimethoxyphenyl)benzeneethanamine

To a cooled (0°C) solution of (1R,2S)-(-)-norephedrine (2.65 g, 17.5 mmole, 2.5 eq) in anhydrous THF (25 mL) was added BH₃-THF complex (35 mL, 35 mmol, 1.0 M solution in THF) dropwise under nitrogen atmosphere. After warming to room temperature and stirring for 20 minutes, a solution of anti-1-(3,4-dimethoxyphenyl)-2-phenylethanone, O-methyloxime (see Washburn *et al.*, EP 0 659 737 A2 for the preparation of this compound) (2 g, 7.34 mmol) in THF (10 mL) was added and then the reaction was refluxed for 2 hours. The reaction was cooled and 1N aq. HCl was added to adjusted the pH to 2.5. The solvent was stripped and the residue was dissolved in water and the solution was basified with 1N aq. NaOH to pH 10. The basic solution was extracted with ether (4 x) and the combined organic layer was washed with brine and dried (anhydrous sodium sulfate) and then filtered. The solvent was stripped and the residue was purified by column chromatography on silica gel (eluent 10% hexanes in ethyl acetate) to give the title compound: $[\alpha]_D = +69.8$ (MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.19 (m, 5H), 6.79-6.86 (m, 3H), 4.14 (dd, 1H, J=8.5, 5.1 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 2.95 (dd, 1H, J=13.3, 5.1 Hz), 2.79 (dd, 1H, J=13.3, 8.5 Hz).

EXAMPLE 8



Preparation of (R)-N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(6-aminopyrin-3-yl)-ethylamine

Step A: (R)-N-[1-(3,4-dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)-ethylamine

5 A solution of 0.178 g (1 mmol) of (R)-2-(tetrazolo[1,5-a]pyrid-6-yl)oxirane (see Fisher and Wyvrat, EP 0 318 092 A2 for the synthesis of this compound) and 0.518 g (2 mmol) of α -(3,4-dimethoxyphenyl)benzeneethanamine in dry methanol (10 mL) was
10 heated at reflux in a gas tight vessel for 14 hours. The reaction mixture was concentrated and the residue was chromatographed on silica gel (5% methanol in methylene chloride) to give the product as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 8.76 (d, 1H, J=15 Hz), 7.91 (dd, 1H, J=9, 3 Hz), 7.41 (t, 1H, J=11 Hz), 7.10-7.32 (m, 5H), 6.77-6.83 (m, 3H),
15 4.51-4.73 (m, 1H), 3.89 (s, 3H, OCH₃), 3.88 and 3.86 (s, 3H, OCH₃), 3.74-3.89 (m, 1H), 2.96-3.0 (m, 1H), 2.84-2.92 (m, 2H), 2.94-2.61 (m, 1H).

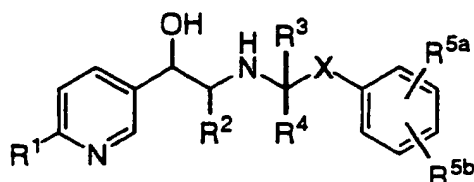
Step B: (R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(6-aminopyrin-3-yl)-ethylamine

20 A mixture of (R)-N-[1-(3,4-Dimethoxyphenyl)-2-phenylethyl]-2-hydroxy-2-(tetrazolo[1,5-a]pyrid-6-yl)ethylamine (104 mg, .25mmol) and tin(II) chloride dihydrate (169 mg, .75 mmol, 3 eq) in methanol (5 mL) was heated at reflux for 14 hours. The reaction
25 mixture was concentrated and the residue was dissolved in a small amount of 20% ammonium hydroxide in methanol and then concentrated to dryness. The residue was purified by preparative thin layer chromatography on silica gel (eluent: 10% methanol, .5% ammonia/methylene chloride) to give the title compound as a white
30 solid: ¹H NMR (500 MHz, CDCl₃) δ 7.91 (s, 1H), 7.10-7.34 (m, 5H), 6.78-6.84 (m, 3H), 6.43 (dd, 1H, J=8.4, 1.8 Hz), 4.40-4.53 (m, 1H), 3.89 and 3.88 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.78-3.89 (m, 1H), 2.90-3.0 (m, 2H), 2.63-2.71 (m, 1H), 2.49-2.59 (m, 1H).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of Formula I

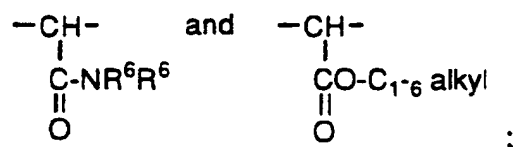


5

I

and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

10 X is a bond or is selected from $-(CH_2)_n-$, $-CH(CN)-$,



n is selected from 1, 2 and 3;

m is selected from zero, 1, 2 and 3;

15 p is selected from zero, 1 and 2;

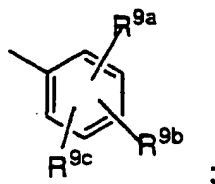
R¹ is selected from

- (1) -H,
- (2) -OH,
- (3) halogen,
- 20 (4) $-NR^8R^8$,
- (5) $-NR^8COR^9$,
- (6) $-NR^8COH$,
- (7) $-NR^8SO_2R^9$, and
- (8) $-N(R^8) \begin{array}{c} CO-C_{1-10} \text{ alkyl} \\ || \\ O \end{array}$;

25

R² is independently selected at each occurrence from -H and -C₁₋₆alkyl;

R³ is selected from -H, -C₁₋₁₂ alkyl, heterocycle and



5

R⁴ is selected from -H, -C₁₋₁₂ alkyl, -CN, -CON(R⁶)R⁶ and -COOC₁₋₆ alkyl;

R^{5a}, R^{5b}, R^{9a}, R^{9b}, and R^{9c} are each independently selected from:

- 10 (1) -H, -C₁₋₁₂ alkoxy, -C₁₋₆ alkyl, halogen, -OH, -CN, -(CH₂)_mN(R²)COC₁₋₆ alkyl, -CON(R²)R², -CON(R²)OR², -CO₂R², -S(O)_p-C₁₋₆ alkyl, -N(R²)SO₂R⁷, -N(R²)R², -OCH₂CON(R²)R², -OCH₂CO₂-C₁₋₆ alkyl, aryl, -CF₃ and -CH₂Y wherein Y is selected from -CN, -C₁₋₁₂ alkoxy, -CON(R²)R², -CO₂R² and -N(R²)SO₂R⁷; or
- 15 (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring, or
- 20 (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring;

25 R⁶ is independently selected at each occurrence from:
-H, -C₁₋₁₂ alkyl, -C₃₋₆ cycloalkyl, aralkyl, aryl and heterocycle, or both R⁶ groups together with the nitrogen to which they are attached may form a 5-10 membered heterocycle;

30 R⁷ is selected from C₁₋₆ alkyl, aryl and aralkyl;

R^8 is independently selected at each occurrence from -H and C₁-10 alkyl;

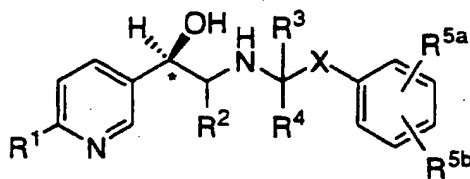
R^9 is selected from C₁-10 alkyl and -NR⁸R⁸;

aryl is selected from phenyl, 1-naphthyl and 2-naphthyl and is
5 unsubstituted or mono- or di-substituted, wherein the substituents are independently selected at each occurrence from R^{5a}; and

heterocycle is an unsubstituted or mono- or di-substituted group selected from:

- 10 (1) a 5 or 6-membered saturated or unsaturated heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and
- 15 (2) a benzene ring fused to a saturated or unsaturated 5 or 6-membered heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and wherein substituents on the heterocycle are independently selected at each occurrence from nitro, keto, 20 azo, thiazo, and R^{5a}.

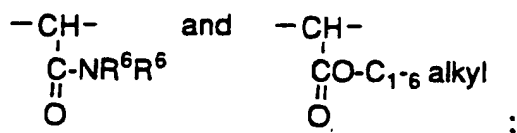
2. The compound of Claim 1 having the Formula Ia



Ia

25 and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is a bond or is selected from -(CH₂)-, -CH(CN)-,

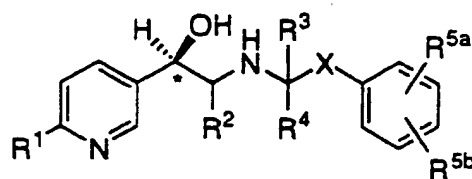


R³ is selected from -H, -C₁-12 alkyl and



R^{5a} and R^{5b} are each independently selected from: -H, halogen, -C₁-12 alkoxy, -C₁-6 alkyl, -CON(R²)R² and -CON(R²)OR².

10 3. The compound of Claim 1 having the Formula Ia

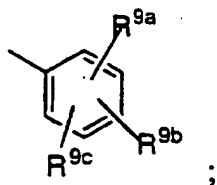


Ia

15 and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is a bond;

R³ is



R⁴ is selected from -H, and -C₁-12 alkyl; and

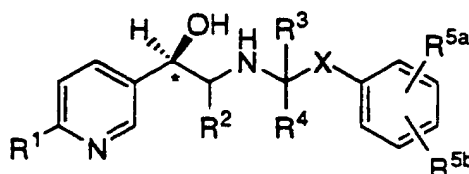
R^{5a} and R^{9a} are each independently selected from:

- (1) -C₁₋₁₂ alkoxy, -OH, -CN, -CON(R²)R², -CON(R²)OR², and -CH₂Y wherein Y is selected from -CN, -C₁₋₁₂ alkoxy, -CON(R²)R², -CO₂R² and -N(R²)SO₂R⁷;

or

- (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring, or
- (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring.

4. The compound of Claim 1 having the Formula Ia



Ia

and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

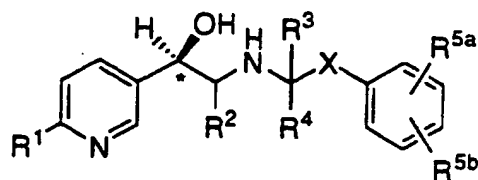
X is a bond;

R³ is selected from -H and -C₁₋₁₂ alkyl;

R⁴ is -CON(R⁶)R⁶; and

R^{5a} is selected from: -C₁₋₁₂ alkoxy, -OH, -CN, -CON(R²)R², and -CON(R²)OR².

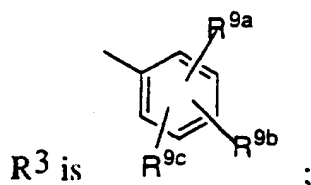
5. The compound of Claim 1 having the Formula Ia



Ia

and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:

X is $-(CH_2)-$;



R⁴ is selected from -H, -C₁₋₁₂ alkyl, -CN and -CON(R⁶)R⁶; and

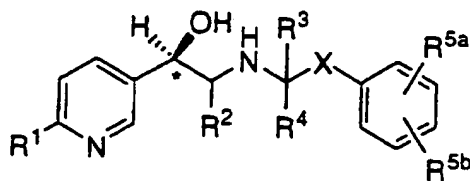
R^{5a} is selected from -H, halogen and -CF₃; and

R^{9a} is selected from

(1) -CN, -CON(R²)R², -CON(R²)OR², -OH, -C₁₋₆ alkyl and -C₁₋₁₂ alkoxy; or

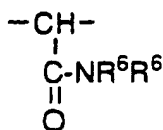
(2) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a phenyl ring or a heterocycle ring.

6. The compound of Claim 1 having the Formula Ia



Ia

and the pharmaceutically acceptable salts, hydrates and stereoisomers thereof wherein:



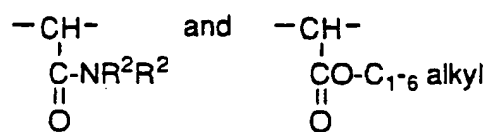
X is selected from -CH(CN)- and ;

R³ and R⁴ are independently selected from -H and -C₁₋₁₂ alkyl; and

5 R^{5a} is selected from: -C₁₋₁₂ alkoxy, -OH, -CN, -CON(R²)R² and -CON(R²)OR².

7. The compound of Claim I wherein:

X is a bond or is selected from -(CH₂)_n-, -CH(CN)-,



10

;

n is selected from 1, 2 and 3;

m is selected from zero, 1, 2 and 3;

p is selected from zero, 1 and 2;

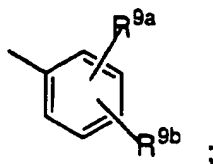
15 R¹ is selected from

- (1) -H,
- (2) -OH,
- (3) halogen,
- (4) -NR⁸R⁸,
- (5) -NR⁸COR⁹,
- (6) -NR⁸COH,
- (7) -NR⁸SO₂R⁹, and
- (8) -N(R⁸) $\begin{array}{c} \text{CO-C}_{1-10} \text{ alkyl} \\ || \\ \text{O} \end{array}$

20

R² is independently selected at each occurrence from -H and
25 -C₁₋₆ alkyl;

R³ is selected from -H, substituted -C₁₋₁₂ alkyl, heterocycle and



- R⁴ is selected from -H, -C₁₋₁₂ alkyl, -CN, -CON(R²)R² and -COOC₁₋₆ alkyl;
- 5 R^{5a}, R^{5b}, R^{9a} and R^{9b} are each independently selected from:
- (1) -H, -C₁₋₁₂ alkoxy, -C₁₋₆ alkyl, halogen, -OH, -CN, -(CH₂)_mN(R²)COC₁₋₆ alkyl, -CON(R²)R², -CO₂C₁₋₆ alkyl, -S(O)_p-C₁₋₆ alkyl, -N(R²)SO₂R⁷, -N(R²)R², -OCH₂CON(R²)R², and -OCH₂CO₂-C₁₋₆ alkyl; or
 - 10 (2) when R^{5a} and R^{5b} are bonded to adjacent carbon atoms, then R^{5a} and R^{5b} together with the carbon atoms to which they are attached may form a heterocycle ring, or
 - (3) when R^{9a} and R^{9b} are bonded to adjacent carbon atoms, then R^{9a} and R^{9b} together with the carbon atoms to which they are attached may form a heterocycle ring;
 - 15
- R⁶ is independently selected at each occurrence from:
- H, -C₁₋₁₂ alkyl, -C₃₋₆ cycloalkyl, aralkyl, aryl and heterocycle, or both R⁶ groups together with the nitrogen to which they are attached may form a 5-10 membered heterocycle;
- 20 R⁷ is selected from C₁₋₆ alkyl, aryl and aralkyl;
- R⁸ is independently selected at each occurrence from -H and C₁₋₁₀ alkyl;
- 25 R⁹ is selected from C₁₋₁₀ alkyl and -NR⁸R⁸;
- aryl is selected from phenyl, 1-naphthyl and 2-naphthyl and is unsubstituted or mono- or di-substituted, wherein the substituents are independently selected at each occurrence from R^{5a}; and
- 30 heterocycle is an unsubstituted or mono- or di-substituted group selected from:

- (1) a 5 or 6-membered saturated or unsaturated heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and
- 5 (2) a benzene ring fused to a saturated or unsaturated 5 or 6-membered heterocyclic ring comprised of carbon atoms and from 1 to 4 heteroatoms independently selected from -O-, -S-, -N- and -NH-, and wherein substituents on the heterocycle are
- 10 independently selected at each occurrence from nitro, keto, azo, thiazo, and R^{5a}.

8. A compound of Claim 1 selected from the group:
- 15 N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- α -[[[(R)-2-hydroxy-2-(pyridin-3-yl)ethyl]amino]methyl]-N,N-dimethylbenzeneacetamide;
- 20 α -[[[(R)-2-hydroxy-2-(2-chloropyrid-5-yl)ethyl]amino]methyl]-N,N-dimethylbenzeneacetamide;
- (R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- (R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-
- 25 3-yl-ethylamine;
- (R),(R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- (R),(R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;
- 30 (R),(S)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(chloropyrid-5-yl)-ethylamine;
- (R),(S)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-pyridin-3-yl-ethylamine;

N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(6-aminopyridin-3-yl)-ethylamine; and
(R)-N-[1-(3,4)-dimethoxyphenyl]-2-phenylethyl]-2-hydroxy-2-(6-aminopyridin-3-yl)-ethylamine.

5

9. A method for the treatment of diabetes which comprises administering to a diabetic patient a therapeutically effective amount of a compound of Claim 1.

10

10. A method for the treatment of obesity which comprises administering to an obese patient a therapeutically effective amount of a compound of Claim 1.

15

11. A method for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels which comprises administering to a patient needing lower triglyceride and cholesterol levels or higher high density lipoprotein levels a therapeutically effective amount of a compound of Claim 1.

20

12. A method for treating atherosclerotic disease which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of Claim 1.

25

13. A method for decreasing intestinal motility which comprises administering to a patient in need of decreased intestinal motility, a therapeutically effective amount of a compound of Claim 1.

30

14. A method for reducing neurogenic inflammation of airways which comprises administering to a patient in need of reduced neurogenic inflammation, a therapeutically effective amount of a compound of Claim 1.

15. A method for treating depression which comprises administering to a depressed patient a therapeutically effective amount of a compound of Claim 1.

5 16. A method for treating gastrointestinal disorders which comprises administering to a patient with gastrointestinal disorders a therapeutically effective amount of a compound of Claim 1.

10 17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 and an inert carrier.



Application No: GB 9619331.3
Claims searched: 1-17

Examiner: Stephen Quick
Date of search: 18 December 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): (not searched)

Int Cl (Ed.6): (not searched)

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X,P	WO95/29159 A1 (MERCK), see whole document, eg examples 6, 7, 9, 10, 17 & 18 at least	1-17
X	WO94/29290 A1 (PFIZER), see whole document, especially examples 116 & 117 and page 27 line 19ff	1-17
X	US4906645 A (MERCK), see whole document, especially examples 3, 6, 9, 12, 15 & 18	1-8
X	US4863939 A (BAYER), see whole document, especially examples 1 & 5 (column 25) and column 8 (1st table, last entry)	1-8
X	US4800206 A (HOFFMANN-LA ROCHE), see whole document, especially examples 15(A)(a) & 15(B) and columns 5 (line 41ff) & 6 (line 30ff)	1-17
X	US4358455 A (MERCK), see whole document, especially examples 4E, 5B, 7D, 7E, 8A & 8B and column 5 line 34ff	1-8 & 17

X Document indicating lack of novelty or inventive step
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